

Remarks

Claims 1-59 are pending in the subject application. Applicant acknowledges that claims 14-31 and 58-59 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicant has canceled claims 14-31, 58, and 59, amended claims 1, 6, 10-13, 32, 37, 41-45, 50, and 54-57, and added new claims 60-69. Support for the new claims and the amendments to the pending claims can be found throughout the subject specification including, for example, at page 5, line 29 through to page 6, line 1; page 8, lines 2-4; page 8, lines 28-31; page 9, line 29 through to page 10, line 5; page 10, lines 19-24; and page 11, lines 18-25. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-13, 32-57, and 60-69 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54, and 57 are rejected under 35 USC §103(a) as obvious over Zerhusen *et al.* (1999) in view of Fields *et al.* (U.S. Patent No. 5,667,973). Zerhusen *et al.* is cited as teaching that CFTR forms dimers. Fields *et al.* is cited as teaching that the interaction of two polypeptides can be detected by the method of the yeast two-hybrid system. The Examiner states that these references taken together would make it obvious to one skilled in the art to detect the interaction of CFTR proteins in the yeast two-hybrid system. Applicant respectfully traverses this ground of rejection.

Applicant respectfully asserts that the cited references do not teach or suggest the claimed invention. Although the Zerhusen *et al.* reference may provide some evidence that CFTR forms dimers, the ordinarily skilled artisan would not know which domains of CFTR are involved in dimer formation. CFTR is a very large polypeptide comprising 1480 amino acids and that has multiple transmembrane and cytosolic domains, any which of could be involved in dimer formation between two CFTR polypeptides. To test for interaction between various CFTR domains in the two-hybrid system would require the subcloning of a wide range of different CFTR domains into the appropriate GAL4 binding domain vector, and co-expression with all possible combinations of the same set of domains expressed with the GAL4 activation domain. By this Amendment, Applicant has amended the claims to recite that the CFTR polypeptide of the fusion protein in the claimed invention

comprises the NBD1 domain of CFTR. There is no teaching or suggestion in any of the cited references to use the NBD1 domain or that the NBD1 domain is important for CFTR interaction and dimer formation. In fact, at page 7630, end of the second paragraph, the authors of the Zerhusen *et al.* reference indicate that it was still unknown what regions of a CFTR protein were involved in protein interaction and dimer formation when they posed the question "...which portions of the CFTR molecule are involved in the contact interaction ..?"

The Zerhusen *et al.* reference additionally teaches the formation of a CFTR dimer that is in a head-to-tail configuration, which has since been shown to be incorrect. The head-to-tail configuration of the Zerhusen *et al.* constructs would require CFTR dimers form whereby an NBD1 domain is positioned adjacent to an NBD2 domain. However, a publication by Schillers *et al.* ("Imaging CFTR: A Tail to Tail Dimer with a Central Pore," 2004, *Cell Physiol. Biochem.*, Vol. 14:1-2, pp. 1-10), a copy of which is enclosed with this Amendment, teaches that CFTR dimers would be arranged in a head-to-head or tail-to-tail configuration. This configuration would predict that an NBD1 domain should be aligned with an NBD1 domain in a dimer of CFTR, consistent with the present invention. The results of the Zerhusen *et al.* reference teach away from the present invention by suggesting CFTR dimer formation wherein the ordinarily skilled artisan would predict that an NBD1 domain of one CFTR protein interacts with an NBD2 domain of another CFTR protein. Thus, the results in the Zerhusen *et al.* reference are inconsistent with NBD1-NBD1 involvement in CFTR dimerization.

Applicant also respectfully asserts that, even in light of the teachings of the Zerhusen *et al.* reference, there was debate in the scientific community at the time of the present invention as to whether CFTR proteins formed monomers or dimers. A publication by Marshall *et al.* ("Stoichiometry of Recombinant Cystic Fibrosis Transmembrane Conductance Regulator in Epithelial Cells and its Functional Reconstitution into Cells *in vitro*," 1994, *Journal of Biological Chemistry*, Vol. 269(4), pp. 2987-2995), a copy of which is enclosed with this Amendment, provided evidence at the time of the present invention that CFTR does not interact to form dimers, but rather functions as a monomer. Thus, the question of whether CFTR exists as a monomer or a dimer was not definitively settled at the time of the filing of the present application.

In view of the above remarks, Applicant respectfully asserts that the cited references do not teach or suggest the claimed invention and a person of ordinary skill in the art would not have had a reasonable expectation of success in arriving at Applicant's claimed invention. At best, the references cited by the Examiner may have made it "obvious to try" CTFR protein in a yeast two-hybrid system. However, it is well settled in U.S. patent law that "obvious to try" is not the appropriate standard for determining obviousness under 35 USC §103. *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987). Therefore, it would not be obvious to one skilled in the art that NBD1 domains can interact and mediate dimer formation in a yeast two-hybrid system as there was no teaching or suggestion in the cited references as to the involvement of NBD1 domains in dimerization and because there was ample evidence suggesting functional CFTR to be a monomer rather than a dimer. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

Claims 1-10, 13, 32-41, 44-54, and 57 are rejected under 35 USC §103(a) as obvious over Zerhusen *et al.* (1999) and Fields *et al.* (U.S. Patent No. 5,667,973), and further in view of Payan *et al.* (U.S. Patent No. 6,316,223). Zerhusen *et al.* and Fields *et al.* are cited for their teachings as before. The Payan *et al.* patent is cited as teaching a two-hybrid system that can be used in mammalian cells. Applicant respectfully traverses this ground of rejection.

Applicant respectfully asserts that the cited references do not teach or suggest the claimed invention. In regard to the primary references cited by the Examiner under this rejection, Zerhusen *et al.* and Fields *et al.*, Applicant respectfully reasserts the remarks in their entirety set forth previously in this Amendment under the rejection of claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54, and 57 for obviousness over Zerhusen *et al.* and Fields *et al.*

The secondary reference cited by the Examiner under this rejection does not cure the deficiencies of the primary references. The Payan *et al.* reference does not teach or suggest anything concerning CFTR proteins and interaction or dimerization thereof. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

Claims 1-3, 5-13, 32-34, 36-47, and 49-57 are rejected under 35 USC §103(a) as obvious over Zerhusen *et al.* (1999) in view of Fields *et al.* (U.S. Patent No. 5,667,973), and further in view of Neville *et al.* (1998). Zerhusen *et al.* and Fields *et al.* are cited for their teachings as before. The

Neville *et al.* reference is cited as teaching that CFTR protein interaction occurs at the NBD1 domain and is affected by the $\Delta F508$ mutation. Applicant respectfully traverses this ground of rejection.

Applicant respectfully asserts that the cited references do not teach or suggest the claimed invention. In regard to the primary references cited by the Examiner under this rejection, Zerhusen *et al.* and Fields *et al.*, Applicant respectfully reasserts the remarks in their entirety set forth previously in this Amendment under the rejection of claims 1-3, 5-10, 13, 32-34, 36-41, 44-47, 49-54, and 57 for obviousness over Zerhusen *et al.* and Fields *et al.*

The secondary reference cited by the Examiner under this rejection does not cure the deficiencies of the primary references. The Neville *et al.* reference does not teach or suggest CFTR protein-protein interaction, but rather is directed to NBD1 and R domain interactions. Moreover, there is no teaching regarding NBD1 interaction with NBD1 or involvement in dimer formation (the Examiner acknowledges under this rejection that the Zerhusen *et al.* reference does not teach the examination of the $\Delta F508$ CFTR mutation or CFTR protein-protein interaction or dimerization). The Neville *et al.* reference only teaches an interaction between NBD1 and R domains. In addition, and contrary to the Examiner's assertion, Applicant was unable to find any results in the Neville *et al.* reference that showed that the $\Delta F508$ mutation affected NBD1 and R domain interaction. See, for example, page 2408, left column, lines 7-10 of the Neville *et al.* reference wherein the authors state "The absence of an effect of the $\Delta F508$ mutation is consistent with previous studies showing similar thermodynamic stability and nucleotide binding affinity for the wild-type vs. $\Delta F508$ isolated NBD1 domain." Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicant's agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Enclosures: copy of Schillers *et al.* (2004) and Marshall *et al.* (1994) references